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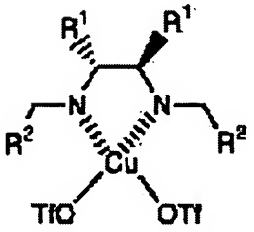
(54) NEW CHIRAL COPPER CATALYST AND METHOD FOR MANUFACTURING N-ACYLATED AMINOACID DERIVATIVE BY USING THE SAME

(57)Abstract:
PROBLEM TO BE SOLVED: To provide a catalyst system which makes efficient, easy and stereoselective Mannich reaction possible from an N-acylimino ester as the starting material.
SOLUTION: A new chiral copper catalyst expressed by formula (I) is used. In formula (I), R1 and R2 are same or different groups and each represents an aromatic hydrocarbon group which may have a substituent.



(1)

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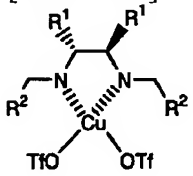
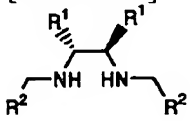
CLAIMS

[Claim(s)]
[Claim 1] Degree type (I)
[Formula 1]



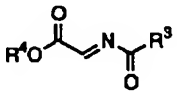
(I)

It is the new chiral copper catalyst characterized by what is expressed with (however, R1 and R2 are the same or the aromatic hydrocarbon radical which may have the substituent in another **).
[Claim 2] Trifluoro methansulfonic acid copper and a degree type (II)
[Formula 2]



(II)

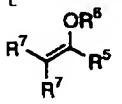
It is the new chiral copper catalyst which mixes the ligand expressed with (however, R1 and R2 are the same or the aromatic hydrocarbon radical which may have the substituent in another **), and is acquired.
[Claim 3] R1 is one new chiral copper catalyst of claims 1 or 2 which are phenyl groups.
[Claim 4] R2 is claim 1 which is 1-naphthyl group thru/or one new chiral copper catalyst of 3.
[Claim 5] It is the approach of manufacturing N-acylation amino acid derivative enantioselective, and is a degree type (III).
[Formula 3]



(III)

It is [N-acyl imino ester expressed with (however, R3 and R4 are the same or the chain-like hydrocarbon group which may have the substituent in another **), and] a degree type (IV).

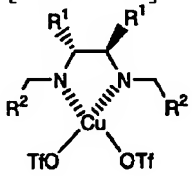
[Formula 4]



(IV)

It is a degree type (I) about the silyl enol ether expressed with (however, being the hydrocarbon group in which R7 may have the hydrogen atom or the substituent [6 / aromatic hydrocarbon radical / on which R5 may have substituent /, and / R/ trialkylsilyl group]).

[Formula 5]

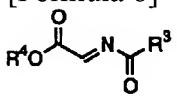


(I)

It is the manufacture approach of N-acylation amino acid derivative characterized by making it react to the bottom of existence of the chiral copper catalyst expressed with (however, R1 and R2 are the same or the aromatic hydrocarbon radical which may have the substituent in another **).

[Claim 6] It is the approach of manufacturing N-acylation amino acid derivative enantioselective, and is a degree type (III).

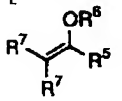
[Formula 6]



(III)

It is [N-acyl imino ester expressed with (however, R3 and R4 are the same or the chain-like hydrocarbon group which may have the substituent in another **), and] a degree type (IV).

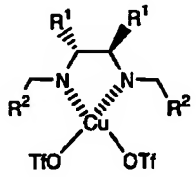
[Formula 7]



(IV)

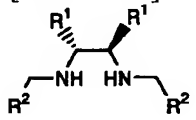
It is a degree type (I) about the alkyl vinyl enol ether expressed with (however, being the hydrocarbon group in which R7 may have the hydrogen atom or the substituent [6 / aromatic hydrocarbon radical / on which R5 may have substituent /, and / R/ alkyl group]).

[Formula 8]



(I)

It is the manufacture approach of N-acylation amino acid derivative characterized by making it react to the bottom of existence of the chiral copper catalyst expressed with (however, R1 and R2 are the same or the aromatic hydrocarbon radical which may have the substituent in another **), and carrying out acid treatment.
[Claim 7] A chiral copper catalyst is trifluoro methansulfonic acid copper and a degree type (II).
[Formula 9]



(II)

It is the manufacture approach of one N-acylation amino acid derivative of claims 5 or 6 which mix the ligand expressed with (however, R1 and R2 are the same or the aromatic hydrocarbon radical which may have the substituent in another **), and are obtained.
[Claim 8] It is the manufacture approach of claim 5 whose R1 is a phenyl group in a chiral copper catalyst thru/or one N-acylation amino acid derivative of 7.
[Claim 9] It is the manufacture approach of claim 5 whose R2 is 1-naphthyl group in a chiral copper catalyst thru/or one N-acylation amino acid derivative of 8.

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention] Invention of this application relates to the manufacture approach of N-acylation amino acid derivative using a new copper catalyst and new it. further -- detailed -- invention of this application -- a new chiral copper complex and it -- using -- enantioselectivity -- it is related with the dissymmetry Mannich mold reaction which manufactures N-acylation amino acid derivative highly.
[0002]
[Description of the Prior Art] Many important N-acetylamino acid derivatives exist in a nature. For example Calcium antagonism nature Dutch algae Scytonema sp. which it has Scytonemin A (Helms, G.L; Moore, R.E., Niemczura, W.P., Patterson, G.M.L., Tomer, and KB. --) which is the main metabolite of (strain U-3-3) Gross, M.L., J.Org.Chem.1998, 53, 1298, Theonellamide F (Matusnaga, S., Fusetani, N., Hashimoto, K., Walchli, and M. --) which is the antibacterial peptide of the sea student sponge origin of a Theonella group J. Am.Chem.Soc.1989, 111, 2582, The thing of many including sphingolipid (Dickson, R.C.Annu.Rev.Biochem.1998, 67, 27) isolates. it is reported (Humphrey and .M. --) Chamberlin, A.R., and Chem.Rev. 1997, 97, 2243; von Dohren, H., and Keller, U., Vater, J., Zocher, R.Chem.Rev.1997, 97, 2675; Koltr, T., Sandhoff, K.Angew.Chem., Int.Ed.1999, 38, 1532, etc.
[0003] The artificers of this application act on the sphingomyelin (SM) composition in an

animal cell specifically especially. Are reported as matter which controls the intracellular transport of sphingolipid. N-(3-Hydroxy-1-hydroxymethyl-3-phenylpropyl) dodecanamide (HPA-12) (it Ueno(es) Yasuda, S., Kitagawa, and H. --) of a ceramide analog M., Ishitani, H., Fukasawa, M., Nishijima, M., Kobayashi, S, Hanada, K.J.Biol.Chem.2001, 276, and 43994-44002 were observed. such matter -- stereoselectivity -- if highly compoundable, it acts as an inhibitor of the ceramide transportation to an endoplasmic reticulum from (Sphingomyelin SM) composition site, and it is expected that it becomes possible to control cell death.

[0004] As an approach of producing a natural compound like HPA-12, and its analogue by chemosynthesis, the stereoselective Mannich mold reaction (Kobayashi, S., Ishitani, H.Chem.Rev.1999, 99, 1069) of alpha-imino ester and enolate is efficient. Artificers develop the stereoselective Mannich mold reaction approach by the zirconium catalyst recently. it has reported (Ishitani and H. --) Ueno, M., and Kobayashi, S.J.Am.Chem.SOc.1997, 119 7153; Kobayashi, S., Ishitani, H., and Ueno, M.J.Am.Chem.Soc.1998, 120 431; Ishitani, H., Ueno, M., and Kobayashi, S.J.Am.Chem.Soc.2000, 122 8180; Kobayashi, S., Ishitani, H., Yamashita, Y., Ueno, M., Shimizu, H.Tetrahedron 2001, 57, 861. Moreover, many reports are made also about the dissymmetry Mannich reaction of alpha-imino ester. (For example) Hagiwara, E., and Fujii, A., Sodeoka, M.J.Am.Chem.Soc.1998, 120, 2474; Ferraris, D., Young, B., Dudding, T., Lectka, and T.J.Org.Chem. Others [2168 / 1999, 64, and].

[0005] However, it was what needs to remove N-protective group from a product, and needs to acylate further, and these well-known reaction approach takes complicated actuation.

[0006] Then, the method of making N-acyl imino ester react with enolate, and obtaining N-acylation amino acid derivative directly as the more efficient reaction approach, was examined. However, the actual condition is that many of N-acyl imino ester used as starting material is unstable, and the applicability of organic synthesis was limited.

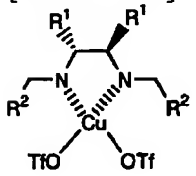
[0007] Therefore, invention of this application solves the trouble as above, and makes it the technical problem to offer the catalyst system which enables the efficient and simple stereoselective Mannich mold reaction which uses N-acyl imino ester as starting material. Moreover, invention of this application acts using such a catalyst as an inhibitor of the ceramide transportation to an endoplasmic reticulum from a sphingomyelin composition site, and also offers the manufacture approach of N-acylation amino acid derivatives including N(R [1], 3R)-(3-hydroxy-1-hydroxymethyl-3-phenylpropyl) dodecane amide (HPA-12) which controls cell death.

[0008]

[Means for Solving the Problem] Invention of this application is a degree type (I) in the 1st first as what solves the technical problem as above.

[0009]

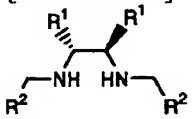
[Formula 10]



(I)

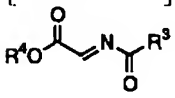
[0010] The new chiral copper catalyst characterized by what is expressed with (however,

R1 and R2 are the same or the aromatic hydrocarbon radical which may have the substituent in another **) is offered.
[0011] In the 2nd, invention of this application is trifluoro methansulfonic acid copper and a degree type (II).
[0012]
[Formula 11]



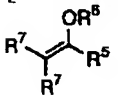
(II)

[0013] The new chiral copper catalyst which mixes the ligand expressed with (however, R1 and R2 are the same or the aromatic hydrocarbon radical which may have the substituent in another **), and is acquired is offered.
[0014] Moreover, invention of this application provides the 3rd with said one whose R2 is 1-naphthyl group the 4th about said one whose R1 is a phenyl group of new chiral copper catalysts of new chiral copper catalysts.
[0015] Furthermore, invention of this application is the approach of manufacturing N-acylation amino acid derivative enantioselective to the 5th, and is a degree type (III).
[0016]
[Formula 12]



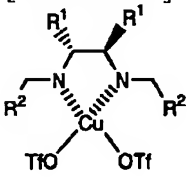
(III)

[0017] It is [N-acyl imino ester expressed with (however, R3 and R4 are the same or the chain-like hydrocarbon group which may have the substituent in another **), and] a degree type (IV).
[0018]
[Formula 13]



(IV)

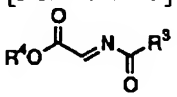
[0019] It is a degree type (I) about the silyl enol ether expressed with (however, being the hydrocarbon group in which R7 may have the hydrogen atom or the substituent [6 / aromatic hydrocarbon radical / on which R5 may have substituent /, and / R/ trialkylsilyl group]).
[0020]
[Formula 14]



(I)

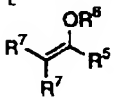
[0021] The manufacture approach of N-acylation amino acid derivative characterized by making it react to the bottom of existence of the chiral copper catalyst expressed with (however, R1 and R2 are the same or the aromatic hydrocarbon radical which may have

the substituent in another **) is offered.
[0022] Invention of this application is the approach of manufacturing N-acylation amino acid derivative enantioselective to the 6th, and is a degree type (III) again.
[0023]
[Formula 15]



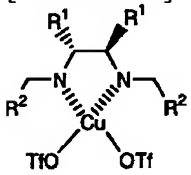
(III)

[0024] It is [N-acyl imino ester expressed with (however, R3 and R4 are the same or the chain-like hydrocarbon group which may have the substituent in another **), and] a degree type (IV).
[0025]
[Formula 16]



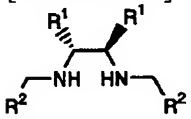
(IV)

[0026] It is a degree type (I) about the alkyl vinyl enol ether expressed with (however, being the hydrocarbon group in which R7 may have the hydrogen atom or the substituent [6 / aromatic hydrocarbon radical / on which R5 may have substituent /, and / R/ alkyl group]).
[0027]
[Formula 17]



(I)

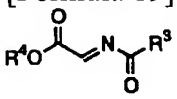
[0028] It is made to react to the bottom of existence of the chiral copper catalyst expressed with (however, R1 and R2 are the same or the aromatic hydrocarbon radical which may have the substituent in another **), and the manufacture approach of N-acylation amino acid derivative characterized by carrying out acid treatment is offered.
[0029] For invention of this application, in the 7th, a chiral copper catalyst is trifluoro methansulfonic acid copper and a degree type (II).
[0030]
[Formula 18]



(II)

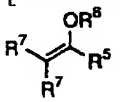
[0031] The manufacture approach of one which mixes the ligand expressed with (however, R1 and R2 are the same or the aromatic hydrocarbon radical which may have the substituent in another **), and is obtained of said N-acylation amino acid derivatives is offered.
[0032] And invention of this application provides the 8th also with the manufacture approach of one of said N-acylation amino acid derivatives that R2 is [in / in the 9th / a

chiral copper catalyst] 1-naphthyl group about the manufacture approach of one of said N-acylation amino acid derivatives that R1 is a phenyl group, in a chiral copper catalyst.
[0033]
[Embodiment of the Invention] By invention of this application, it is a degree type (III) first.
[0034]
[Formula 19]



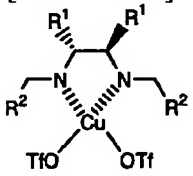
(III)

[0035] It is [N-acyl imino ester expressed with (however, R3 and R4 are the same or the chain-like hydrocarbon group which may have the substituent in another **), and] a degree type (IV).
[0036]
[Formula 20]



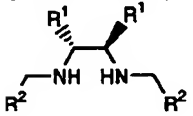
(IV)

[0037] It is a degree type (I) about the silyl enol ether expressed with (however, being the hydrocarbon group in which R7 may have the hydrogen atom or the substituent [6 / aromatic hydrocarbon radical / on which R5 may have substituent /, and / R/ trialkylsilyl group]).
[0038]
[Formula 21]



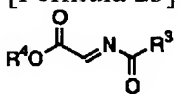
(I)

[0039] N-acylation amino acid derivative is manufactured enantioselective by making it react to the bottom of existence of the new chiral copper catalyst expressed with (however, R1 and R2 are the same or the aromatic hydrocarbon radical which may have the substituent in another **). moreover -- if acid treatment is carried out after making it react to the bottom of existence of N-acyl imino ester and the aforementioned chiral copper catalyst when R6 in the above (IV) uses the alkyl vinyl ether which is an alkyl group instead of the silyl enol ether -- enantioselectivity -- N-acylation amino acid derivative is manufactured highly.
[0040] This new chiral copper catalyst (I) is trifluoro methansulfonic acid copper and a degree type (II).
[0041]
[Formula 22]



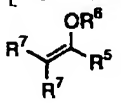
(II)

[0042] It comes out, and the ligand expressed is mixed for example, in a solution, it is obtained, and what was isolated may be used as a catalyst, and in a reaction solution, by in situ, complexing may be carried out and you may prepare.
[0043] In the new chiral copper catalyst (I) of invention of this application, R1 and R2 are the same or the aromatic hydrocarbon radical which may have the substituent in another **, and they are not limited especially. Specifically, the aromatic hydrocarbon radical which has substituents, such as aromatic hydrocarbon radical [, such as a phenyl group, 1-naphthyl group, and 2-naphthyl group,] or 4-methylphenyl radical, 3, 5-dimethylphenyl radical, 3, 5-JI t buthylphenyl radical, 4-chlorophenyl radical, 3, and 5-dichlorophenyl radical, is illustrated preferably. According to research of artificers, the yield and enantioselectivity of a product in a dissymmetry Mannich mold reaction become high, and especially the new chiral copper catalyst whose R2 R1 is 1-naphthyl group in a phenyl group has them so that clearly also from the below-mentioned example.
[desirable]
[0044] It sets to the manufacture approach of N-acylation amino acid derivative invention this application, and is a degree type (III).
[0045]
[Formula 23]



(III)

[0046] Each of R3 and R4 in ** N-acyl imino ester is a chain-like hydrocarbon group, and alkyl groups, such as methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, and t-butyl, are illustrated. What is necessary is just to choose these substituents suitably according to N-acylation amino acid derivative made into the purpose, since it is reflected in N-acylation amino acid derivative which is the product of a dissymmetry Mannich mold reaction. For example, what is necessary is just to set R3 to C11H23, in generating the below-mentioned HPA-12. On the other hand, although it is not limited about R4 especially if it does not become the failure of a reaction, it can consider, for example as short chain alkyl groups, such as methyl and ethyl.
[0047] For the manufacture approach of N-acylation amino acid derivative invention this application, the aforementioned N-acyl imino ester is a degree type (IV).
[0048]
[Formula 24]



(IV)

[0049] It reacts with ********. At this time, in (IV), R5 is the aromatic hydrocarbon radical which may have the substituent, and, specifically, phenyl, 1-naphthyl, 2-naphthyl, 4-methylphenyl, 3, 5-dimethylphenyl, 4-chlorophenyl, etc. are illustrated. Moreover, R7 may be a hydrogen atom and is chosen from hydrocarbon groups, such as alkyl groups, such as methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, and t-butyl, a cyclohexyl radical, and a phenyl group, and the radical which hetero atoms and substituents, such as a halogen, and S, N, O, combined with these. On the other hand, about R6, it can also consider as trialkylsilyl groups, such as a trimethylsilyl radical and a triethyl silyl radical, and is good also as alkyl groups, such as methyl, ethyl, n-propyl, i-propyl, n-butyl, i-

butyl, and t-butyl. When R6 is the trialkylsilyl ether, (IV) serves as the silyl enol ether and, in the case of an alkyl group, (IV) serves as alkyl vinyl ether. In (IV), since especially R5 remains in N-acylation amino acid derivative of a product after a dissymmetry Mannich reaction, it should just choose R5 suitably according to N-acylation amino acid derivative made into the purpose. For example, what is necessary is just to let R5 be a phenyl group, if the below-mentioned HPA-12 are made into the last specified substance.

[0050] In the manufacture approach of N-acylation amino acid derivative invention this application, what is compounded and isolated by the thing and the well-known organic synthesis approach which are marketed as a reagent may be used for N-acyl imino ester which is a reactant, and the silyl enol ether (or alkyl vinyl ether), and may be compounded and used for them by in situ on the occasion of a Mannich mold reaction about what has difficult isolation of a compound, or an unstable thing.

[0051] Furthermore, in the manufacture approach of N-acylation amino acid derivative invention this application, especially that reaction condition is not limited that what is necessary is just that to which a Mannich mold reaction is performed under existence of the aforementioned new chiral copper catalyst. For example, as for a reaction, it is desirable to be carried out in various kinds of organic solvents. A solvent is not limited [that what is necessary is just what can dissolve N-acyl imino ester which is starting material, and the silyl enol ether (or alkyl vinyl ether) and a catalyst] especially that what is necessary is just what is not solidified or decomposed in reaction temperature. For example, halogen-containing solvents, such as chloroform and dichloromethane, etc. are illustrated. the temperature requirement where each reacting matter of reaction temperature is stable, and a catalyst acts efficiently especially -- it is -- ****ing -- desirable -- the low temperature below a room temperature -- it considers as -100 degrees C - room temperature extent more preferably. Furthermore, about concrete reaction actuation, actuation of stirring carried out in a general chemical reaction, separation, purification, etc. is applicable.

[0052] Hereafter, an example is shown and invention of this application is further explained to a detail. Of course, it cannot be overemphasized that invention of this application is not what is limited to the following examples.

[0053]

[Example] The melting point was displayed in the following examples, without amending.

[0054] Moreover, 1H and a carbon-magnetic-resonance spectrum were measured in CDCl3 by JEOL JNM-LA300, JNM-LA400, or 500 spectrometer JNM-LA, unless it mentioned specially. In 1H, the tetramethylsilane (TMS) was used as an internal standard (delta= 0). Moreover, in 13C, CDCl3 was used as an internal standard (delta= 77.0).

[0055] The IR spectrum was measured using -610 spectrometer JASCO FT/IR.

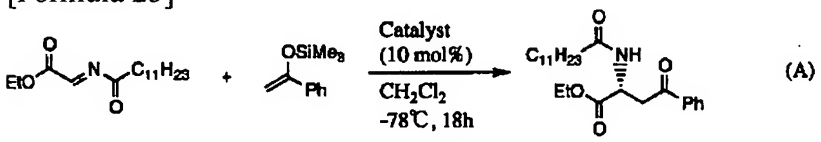
[0056] Circle optical activity was measured with JASCO P-1010 polarimeter.

[0057] High performance chromatography was performed using SHIMADZU LC-10AT (liquid chromatograph), SHIMADZU SPD-10A (ultraviolet-rays detector), and a SHIMADZU C-R6A chromato pack.

[0058] The gas chromatography and the mass spectrum were measured using SHIMADZU GC-17A and SHIMADZU GCMS-QP5050A.

[0059] A column chromatography is Silica gel 60 (Merck), and thin-layer

chromatography was performed using Wakogel B-5F (Wako Pure Chem).
[0060] Any reaction was performed under the argon using the dried glass device.
[0061] N-acyl imino ester 2a and 2b were obtained from corresponding alpha-chloro glycine derivative (Schmitt, M., Bourguignon, J., Barlin, G.B., Davies, L.P.Aust.J.Chem.1997, 50, 719).
<Example 1> According to the Mannich mold reaction degree type (A) of the silyl enol ether of N-acyl imino ester using a new chiral copper catalyst, and the acetophenone origin, the Mannich mold reaction of the silyl enol ether of N-acyl imino ester and the acetophenone origin was performed.
[0062]
[Formula 25]



(A)

2a 5a

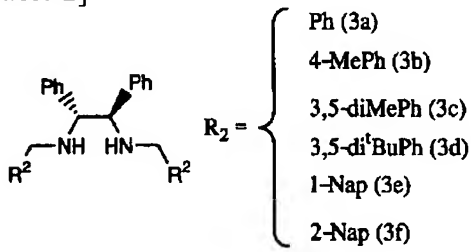
[0063] After drying Cu (OTf)2 (3.6 mg, 0.01 mmol) under a 100-degree C vacuum for 2 hours, the liquid of the light green color which added the dichloromethane (1.0 mL) solution of compound 3e (5.4 mg, 0.0011 mmol) at the room temperature under the argon, and was obtained was stirred for 1.5 hours until it became dark green. The solution was cooled to 0 degree C and the dichloromethane (1.0 mL) solution of the silyl enol ether (0.15mmol) was added.
[0064] Furthermore, it added having covered the dichloromethane (1.0mL) solution of N-acyl imino ester (2a) (0.1mmol) for 20 minutes, and the reaction solution was left at 0 degree C for 18 hours.
[0065] THF-water was added in the reaction solution, the reaction was stopped, and it was warmed to the room temperature after stirring for 2 minutes. The saturation NH4Cl water solution was added into the solution, and it extracted by dichloromethane.
[0066] After salt water washed the organic layer, it dehydrated on sulfuric anhydride magnesium and reduced pressure removal of the solvent was carried out.
[0067] The solvent was removed and dried, after adding dichloromethane (3.0mL) and the dichloromethane solution (1.0 mL) of 0.2N HCl to residue and stirring reaction mixture for 10 minutes at a room temperature.
[0068] Mixture was stirred at the room temperature for 1 hour, and the reaction was suspended by water (5mL) and AcOEt (5ml). After extracting mixed liquor by AcOEt, salt water washed the organic layer and it dehydrated on sulfuric anhydride magnesium.
[0069] After removing a solvent, the silica gel chromatography refined the rough product and compound 5a was obtained.
[0070] The identification result of 5a was shown in Table 1.
[0071]
[Table 1]

Ethyl 2-Dodecanoylamino-4-oxo-4-phenylbutyrate (5a): $[\alpha]^{n}_{D}$ –58.5 (c 1.02, $CHCl_3$); mp 50-51 °C; ^1H NMR ($CDCl_3$) δ = 0.88 (t, 3H, *J* = 6.8 Hz), 1.2-1.4 (m, 19H), 1.5-1.7 (m, 2H), 2.21 (dt, 2H, *J* = 2.4, 7.7 Hz), 3.60 (dd, 1H, *J* = 4.1, 18.3), 3.75 (dd, 1H, *J* = 4.1, 18.3), 4.21 (q, 2H, *J* = 7.1 Hz), 4.96 (dt, 1H, *J* = 4.1, 8.0 Hz), 6.61 (brd, 1H, *J* = 8.0 Hz), 7.47 (apparent t, 2H, *J* = 7.6 Hz), 7.60 (apparent t, 1H, *J* = 7.3 Hz), 7.94 (apparent d, 2H, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ = 14.0, 14.1, 22.6, 25.5, 29.1, 29.3, 29.4, 29.5, 31.9, 36.5, 40.5, 48.2, 61.7, 128.1, 128.7, 133.7, 136.0, 171.2, 172.9, 198.0; IR (neat) 1683, 1742 cm^{-1}; MS (EI) *z/m* = 403 (M^+); HPLC, Daicel Chiralcel AD, hexane/^{i}PrOH = 19/1, flow rate = 1.0 mL/min : t_R = 21.9 min (*S*), t_R = 26.6 min (*R*).

[0072] The chiral copper catalyst was prepared by having made into the ligand 3a-3f similarly shown in Table 2 instead of 3e, and the dissymmetry Mannich mold reaction was performed. Each chiral copper catalyst, reaction yield, and optical purity were shown in Table 2.

[0073]

[Table 2]

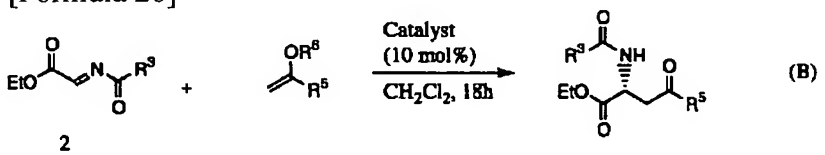


触媒	収率（%）	ee (%)
$Cu(OTf)_2$ + 3a	25	63
$Cu(OTf)_2$ + 3b	32	63
$Cu(OTf)_2$ + 3c	24	75
$Cu(OTf)_2$ + 3d	12	52
$Cu(OTf)_2$ + 3e	20	80
$Cu(OTf)_2$ + 3f	32	64
$Cu(OTf)_2$ + 3e	92	94

[0074] From Table 2, it was shown by by using the new chiral copper catalyst of invention of this application that has various kinds of ligands (II) that N-acylation amino acid derivative is obtained by high enantioselectivity. When the new chiral copper catalyst which has 1-naphthyl group as R2 was used especially, high reaction yield and optical purity were obtained.

According to the <example 2>, next the formula (B), the dissymmetry Mannich mold reaction of various kinds of N-acyl imino ester (2) by the new chiral copper catalyst of

the invention in this application, the silyl enol ether, or vinyl ether was considered.
[0075]
[Formula 26]



2 5

[0076] The reaction was performed by the same approach as an example 1. After drying Cu(OTf) 2 (3.6 mg, 0.01 mmol) under a 100-degree C vacuum for 2 hours, it stirred for 1.5 hours and the catalyst obtained the liquid of the light green color which added the dichloromethane (1.0 mL) solution of compound 3e (5.4 mg, 0.0011 mmol) at the room temperature under the argon, and was obtained until it became dark green.
[0077] By the system which used alkyl vinyl ether, the solvent was removed and dried and the product was obtained, after adding THF (5.0 ml) and 1N HCl water solution (0.25 mL) to residue and stirring reaction mixture for 10 minutes at a room temperature instead of adding dichloromethane (3.0mL) and the dichloromethane solution (1.0 mL) of 0.2N HCl to residue.
[0078] The Products [5b-5d] identification result was shown in Tables 3-5.
[0079]
[Table 3]

Ethyl 2-Dodecanoylamino-4-oxo-4-(4-methoxyphenyl)butyrate (5b): $[\alpha]^{23}_D$ –54.5 (c 0.55, $CHCl_3$); mp 71-72 °C; ^1H NMR ($CDCl_3$) δ = 0.88 (t, 3H, J = 6.8 Hz), 1.2-1.4 (m, 19H), 1.5-1.7 (m, 2H), 2.20 (t, 2H, J = 7.7 Hz), 3.52 (dd, 1H, J = 4.0, 17.9 Hz), 3.71 (dd, 1H, J = 4.0, 17.9 Hz), 3.88 (s, 3H), 4.20 (q, 2H, J = 7.1 Hz), 4.95 (dt, 1H, J = 4.0, 8.1 Hz), 6.62 (d, 1H, J = 8.1 Hz), 6.94 (d, 2H, J = 8.9 Hz), 7.92 (d, 2H, J = 8.9 Hz); ^{13}C NMR ($CDCl_3$) δ =14.0, 14.1, 22.6, 25.5, 29.1, 29.3, 29.4, 29.5, 31.8, 36.5, 40.1, 48.2, 55.5, 61.6, 113.8, 129.1, 130.4, 163.9, 171.3, 172.9, 196.4; IR (neat) 1602, 1675, 1742 cm^{-1}; MS (EI) m/z = 433 (M^+); HPLC, Daicel Chiralcel AD, hexane/^{i}PrOH = 19/1, flow rate = 1.0 mL/min : t_R = 34.8 min (S), t_R = 39.7 min (R).

[0080]
[Table 4]

Ethyl 2-Dodecanoylamino-4-oxo-4-(4-chlorophenyl)butyrate (5c): $[\alpha]^{23}_D$ –49.5 (c 0.51, $CHCl_3$); mp 79-80 °C; ^1H NMR ($CDCl_3$) δ = 0.88 (t, 3H, J = 7.0 Hz), 1.2-1.3 (m, 19H), 1.5-1.7 (m, 2H), 2.21 (dt, 2H, J = 3.4, 7.6 Hz), 3.57 (dd, 1H, J = 4.2, 18.1 Hz), 3.69 (dd, 1H, J = 4.2, 18.1 Hz), 4.21 (q, 2H, J = 7.1 Hz), 4.94 (dt, 1H, J = 4.2, 7.8 Hz), 6.60 (brd, 1H, J = 7.8 Hz), 7.45 (d, 2H, J = 8.6 Hz), 7.88 (d, 2H, J = 8.6 Hz); ^{13}C NMR ($CDCl_3$) δ = 14.0, 14.0 ,22.6, 25.5, 29.1, 29.3, 26.4, 29.5, 31.8, 36.5, 40.4, 48.2, 61.7, 129.0, 129.5, 134.3, 140.2, 171.0, 173.0, 196.8; IR (neat) 1636, 1688, 1732 cm^{-1}; MS (EI) m/z = 437 (M^+); HPLC, Daicel Chiralcel AD, hexane/^{i}PrOH = 19/1, flow rate = 1.0 mL/min : t_R = 21.5 min (S), t_R = 32.7 min (R).

[0081]

[Table 5]

Ethyl 2-acetylamino-4-oxo-4-phenylbutyrate (5d): $[\alpha]^{23}_{D}$ −102.5 (c 0.44, $CHCl_3$); ^1H NMR ($CDCl_3$) δ = 1.23 (t, 3H, *J* = 7.1 Hz), 2.02 (s, 3H), 3.61 (dd, 1H, *J* = 4.1, 18.3), 3.75 (dd, 1H, *J* = 4.1, 18.3), 4.21 (q, 2H, *J* = 7.1), 4.95 (dt, 1H, *J* = 4.1, 7.7), 6.67 (brd, 1H, *J* = 7.7), 7.48 (apparent t, 2H, *J* = 7.6 Hz), 7.60 (apparent t, 1H, *J* = 7.2 Hz), 7.94 (apparent d, 2H, *J* = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ = 14.0, 23.1, 40.5, 48.3, 61.7, 128.1, 128.7, 133.8, 136.0, 169.9, 171.1, 197.9; IR (neat) 1681, 1686, 1744 cm^{-1}; MS (EI) *m/z* = 263 (M^+); HPLC, Daicel Chiralcel AD, hexane/^{i}PrOH = 4/1, flow rate = 1.0 mL/min : t_R = 9.8 min (*S*), t_R = 12.1 min (*R*).

[0082] Moreover, the yield and optical purity of a reaction condition and a product were shown in Table 6.

[0083]

[Table 6]

反応	R^3	R^5	R^6	生成物	収率（%）	ee (%)
1	$C_{11}H_{23}$ (2a)	Ph	$SiMe_3$	5a	92	94
2	$C_{11}H_{23}$ (2a)	MeOPh	$SiMe_3$	5b	97	92
3	$C_{11}H_{23}$ (2a)	ClPh	$SiMe_3$	5c	88	93
4	$C_{11}H_{23}$ (2a)	Ph	Me_3	5a	85	90
5	CH_3 (2b)	Ph	$SiMe_3$	5d	85	94

[0084] From Table 6, it was checked by the manufacture approach of N-acylation amino acid derivative invention this application that N-acylation amino acid derivative is obtained from a ketone, ester, and various kinds of silyl enol ether of the thioester origin by high reaction yield and enantioselectivity. Moreover, the conversion to corresponding N-acylation amino acid derivative advanced also with alkyl vinyl ether.

<Example 3> The synthetic sphingolipid of HPA-12 is the generic name of conjugated lipid which consists of sphingosine which is a long chain base, and a fatty acid, and is the constituent of a biomembrane in a glycerophospholipid and a sterol. After sphingolipid was discovered in the brain extract in 1874, the function has not been clear for years. However, it becomes clear to have contributed to the intracellular signaling of a lipid in recent years, and the importance attracts attention.

[0085] That the fatty acid carried out [that] amide association by two NH(s) is called ceramide, and serves as an intersection of all sphingolipid. Sphingolipid is roughly further divided into sphingoglycolipid and sphingophospholipid by the difference in the hydrophilic group, and what has various structures exists. If ceramide arises from sphingolipid, it will be changed into sphingosine, a glycolipid, ceramide-1-phospholipid, sphingomyelin, etc. through various composition and metabolic systems. The ceramide which exists in a cell envelope mostly, sphingomyelin, and a glycolipid are conveyed to lysosome by endosome, and are decomposed by the enzyme.

[0086] If it is clear that it is an apotosis signal transfer molecule and ceramide makes ceramide introduce into intracellular, fragmentation of DNA, nuclear concentration, fragmentation, etc. will arise and it will start apotosis. Moreover, it is known that apotosis

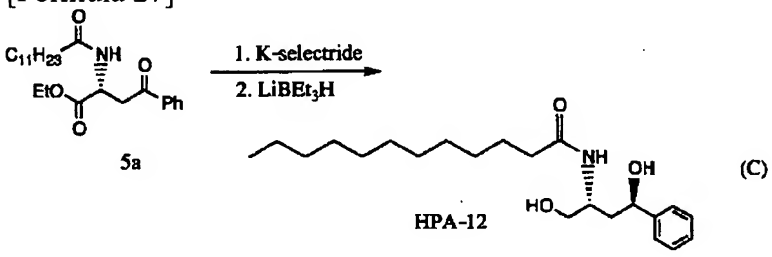
will be caused, even if it decomposes sphingomyelin by intracellular and ceramide is generated.

[0087] Recently as matter which acts as an inhibitor of the ceramide transportation to an endoplasmic reticulum from a sphingomyelin composition site, and controls cell death (1R, 3R) N-(3-hydroxy-1-hydroxymethyl-3-phenylpropyl) dodecane amide (HPA-12) is reported (it Ishitani(s) Yasuda, S., Kitagawa, H., Ueno, and M. --) H., Fukasawa, M., Nishijima, M., Kobayashi, S, Hanada, K.J.Biol.Chem.2001, 276, 43994-44002.

[0088] HPA-12 were compounded according to the degree type (C).

[0089]

[Formula 27]



[0090] The THF solution (0.25 mL, 0.25 mmol) of 1 M K-Selectride was added to the ethylene glycol wood ether solution (0.75 mL) of 5a (20.1 mg, 0.050 mmol) at -45 degrees C. After stirring a mixed solution at -45 degrees C for 2 hours, 1 M super-hydride (0.25 mL) was dropped.

[0091] After warming reaction mixture to a room temperature, it stirred for 1 hour, and water and 30% H2O2 were added, the reaction was suspended, and it extracted by AcOEt. After saturation NaHCO3 solution washed the extract, the water layer was doubled and it extracted by AcOEt. Moreover, salt water washed the organic layer and it dehydrated on anhydrous sodium sulfate.

[0092] After evaporating a solvent, the silica gel chromatography refined residue and HPA-12 were obtained.

[0093] The artificers of this application compounded HPA-12 by the enantioselective Mannich mold reaction which used the chiral zirconium catalyst, and have reported (Ueno, M., Kitagawa, H., Ishitani, H., Yasuda, S., Nishijima, K., Hanada, K., Kobayashi, S.Tetrahedron Lett.2001, 42, 7863). By the approach using such a chiral zirconium catalyst, HPA-12 were obtained at six steps (6.0% of total yield). On the other hand, at the dissymmetry Mannich mold reaction using the new chiral copper complex of the invention in this application, HPA-12 could be compounded at three steps (two pots) from 2a, and total yield was 68.6%.

[0094] Therefore, it is suggested that the synthetic approach of N-acylation amino acid derivative of the invention in this application has the wide application range of various kinds of HPA-12 analogs, and usefulness is high.

[0095] In addition, as for the absolute configuration of 5a, it is reported by artificers that it is R (Ueno, M., Kitagawa, H., Ishitani, H., Yasuda, S., Nishijima, K., Hanada, K., Kobayashi, S.Tetrahedron Lett.2001, 42, 7863).

[0096]

[Effect of the Invention] The manufacture approach of a new chiral copper catalyst and N-acylation amino acid derivative using it is offered by invention of this application as explained in detail above. The approach of this invention makes it possible high yield and

to manufacture enantioselective for N-acylation amino acid derivative at few processes, and is high in composition of various kinds of quality of a natural product, a physiological active substance, or its intermediate field. [of usefulness]